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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NOBLE, MARCIA STEPHENS	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/531,347	SEIBLER ET AL.	
	Examiner	Art Unit	
	MARCIA S. NOBLE	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-40 and 45-48* is/are pending in the application.

4a) Of the above claim(s) *14-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 April 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 14-40 and 45-48 are pending. Claims 14-40 were previously withdrawn from consideration. Claims 41-44 are canceled, and claims 45-48 are newly added by the response filed 1/6/2009. Claims 45-48 are under consideration.

Withdrawn Rejections/Objections

The rejection of claim 41, under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter, as set forth in the Office Action, filed 8/6/2008 (p. 9), is withdrawn.

The rejection of claims 41-43, under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, as set forth in the Office Action mailed 8/6/2008 (pp. 3-4), is withdrawn.

The rejection of claim 44, under 35 U.S.C. 102(b) as being anticipated by Paddison (Genes & Dev 16:948-958, April 2002; of record), as set forth in the Office Action, mailed 8/6/2008 (p. 8), is withdrawn.

The rejection of claims 41-43, under 35 U.S.C. 102(b) as being anticipated by McCaffrey et al. (Nature, 2002 Vol. 418, 38-39), as set forth in the Office Action, mailed 8/6/2008 (pp.8-9), is withdrawn.

The rejection of claims 41-43, under 35 U.S.C. 102(e) as being anticipated by Beach (US patent Publication no. 2003/0084471, publication date 5/1/2003; filing date 1/22/2002), as set forth in the Office Action, mailed 8/6/2008 (pp. 9-10), is withdrawn.

The rejection of claims 41-44, under 35 U.S.C. 103(a) as being unpatentable over Beach et al. (US patent Publication no. 2003/0084471, dated 5/1/2003, effective filing date 1/22/2002); Bronson et al (Proc Natl Acad Sci U S A 1996; 93:9067–9072) and Soriano et al (US patent 6,461,864, October 8, 2002), as set forth in the Office Action, mailed 8/6/2009 (pp. 10-14), is withdrawn.

The objection to the specification for sequence compliance issues in Tables 1 and 2, as set forth in the Office Action, mailed 8/6/2009 (p. 16), is withdrawn.

Claim Rejections - 35 USC § 112, 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Applicant's amendments cancel claims 41-43 and replace them with newly added claims 45-47. These amendments necessitate the following modifications to the enablement rejection:

Claims 45-47, as newly added, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a **mouse** having stably integrated an expression vector comprising a shRNA construct under control of a ubiquitous promoter at a polymerase II dependent locus of the mouse genome by homologous recombination, wherein expression of said shRNA results in repression of expression of a gene targeted by said shRNA in said mouse, does not reasonably provide enablement for 1) a vertebrate other than a mouse having stably integrated said expression vector into a polymerase II dependent locus, and 2) a transgenic vertebrate with no phenotype. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use/make the invention commensurate in scope with these claims.

When determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue".

1) The instant claims broadly embrace the production of any transgenic rodent with a targeted insertion of the transgene into a polymerase II dependent locus by homologous recombination. However, the specification only teaches the production of a mouse comprising a targeted insertion in its genome.

The specification discloses the production of mouse ES cells comprising the firefly luciferase gene inserted into the first allele of the rosa26 locus by homologous recombination. A shRNA expression cassette under the control of the H1 or H6 promoter and a Renilla luciferase gene were inserted into these mouse ES cells at the second allele of the rosa26 locus by homologous recombination (Example 1, p. 18, lines 1-6). The specification discloses that the shRNA expression cassette can also be under the control of U6 promoter containing a tet operator sequence to allow for inducible control of the shRNA expression cassette (Example 2, p. 18, par 3, lines 1-4). The specification discloses that these recombinant mouse ES cell were injected into diploid blastocysts and ultimately produced transgenic mice expressing the shRNA expression vector.

At the time of filing and presently, the art teaches that gene-targeting in vivo required homologous recombination in cells in vitro. The only cells that can be cultured in vitro that are competent to populate the germline and thereby make an animal are mouse ES cells. Thus, ES cell use for the generation of targeted genetically modified animals, such as knockin or knockout animals, has only been established in mice. Denning and Priddle state, "...pluripotent embryonic stem (ES) cells, which have been central to success in mice, are not available in any domestic species, despite

considerable efforts to isolate them." (Reproduction 126:1, col 2, par 1, 2003). Since the art does not teach a means of making targeted insertions by homologous recombination in other species than mice, an artisan would look to the specification for specific guidance from the specification. However, the specification only provides specific guidance for the mouse. Therefore, the specification fails to provide specific guidance to predictably teach a means of making a transgenic vertebrate with a targeted insertion of an expression vector in any other vertebrate than mouse without undue experimentation. The term "rodent", as instantly claimed, encompasses a large genus of mammals. See **"rodent"** . (2009). In *Encyclopædia Britannica*. Retrieved April 22, 2009, from Encyclopædia Britannica Online: http://www.search.eb.com/eb/article-9105980, enclosed herein, which states that rodents encompass more than 2,050 living mammals, including rats and mice, but additionally porcupines, beavers, squirrels, marmots, pocket gophers and chinchillas (see 1st ¶). Thus given that the term "rodent" encompasses a large genus of animals, whereas the state of the art and working example only provides guidance with regard to a transgenic mouse, and that ES cells are not available in any other species of mammal, the enabled scope of the claimed invention has been limited to mouse.

2) The claims encompass a transgenic rodent that lacks a phenotype. The specification teaches that the purpose of the instant invention is to provide knock down animal with the use of shRNA expression vectors (p. 1, lines 1-3). The specification teaches the expression of the shRNA transgene encoding firefly luciferase by the transgenic mouse efficiently represses firefly luciferase activity in most organs (p. 19,

Example 4, last par, lines 7-10). Therefore, the specification provides specific guidance to a transgenic mouse comprising a phenotype. However, the specification fails to provide specific guidance to teach the use of a transgenic rodent with no phenotype as claimed. Therefore, the specification does not provide an enabled use for a transgenic rodent with no phenotype.

Overall, the instant claims are not enabled for the full breadth of the claims because the art at the time of the invention teaches that, with the exclusion of mice, the production of transgenic rodents with a targeted insertion of an expression vector is not predictable. The instant claims are also not enabled for the full breadth of the claims which would encompass a transgenic rodent with no phenotype because the specification fails to provide an enabled use for such a transgenic rodent with no phenotype. Furthermore, the specification fails provide specific guidance to overcome these unpredictabilities in the art. Therefore, the instant claims are only enable for a mouse having stably integrated an expression vector comprising a shRNA construct under control of a ubiquitous promoter at a polymerase II dependent locus of the mouse genome by homologous recombination, wherein expression of said shRNA results in repression of expression of a gene targeted by said shRNA in said mouse.

Applicant's arguments filed 1/6/2009 have been fully considered but they are not persuasive. Applicant asserts that the claims have been amended to encompass rodent, which is enabled subject matter. Applicant asserts that the Examiner concedes enablement for mice and submits that persons skilled in the art would reasonably

expect the invention to be applicable to rodents and be operable therein (p. 19, 1st full par of response).

Applicant's arguments are not found persuasive. Contrary to Applicant's assertion, an artisan would not expect the invention to be applicable to other rodents than mice because the invention requires a targeted insertion by homologous recombination into ES cells and the only competent ES cells for such a targeted insertion with stable integration is mouse ES cell. Other rodent ES cell are not capable of such stable integration of a targeted insertion by homologous recombination. (see Priddle and Denning discussed above). Therefore, an artisan would not expect the instant invention to be operable in other rodents than mice because the art teaches inoperability. Additionally, the term "rodent" encompasses a large genus of animals. Neither the specification, working examples or state of the art supports that the breadth of "rodent" ES cells would be available to produce the transgenic rodents that are claimed in the instant invention. There is no guidance provided the specification with regard, for example, to production of a transgenic porcupine, beaver or squirrel. Furthermore, the specification does not provide any guidance with regard to the phenotype that the breadth of transgenic rodents, encompassed by the claims would have.

It is noted that the claims were also rejected on the grounds that the inventions encompasses a transgenic rodent with no phenotype and the specification does not provide an enabled use for a transgenic rodent that lacks a phenotype. Applicant did

not address this issue of enablement; thus the issue is maintained as previously made of record and reiterated above.

In conclusion, the amended claims still lack enablement because the claims encompass a non-mouse rodent which the art suggests will be inoperable and because the specification does not teach an enabled used for a transgenic rodent lacking a phenotype.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The amendments to the claims necessitate the following modification of the instant rejection:

Claims 45-48 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 27 and 30 of amendment filed 5/30/2008 in copending Application No. 10/685,837. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the copending claims encompass the same scope.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim 45 of the instant invention broadly encompasses a vertebrate having stably integrated, preferably at a polymerase II dependent locus of the vertebrate, an expression vector comprising a short hairpin RNA construct under the control of a ubiquitous promoter. Claim 46 specifies that the vertebrate is a non-human vertebrate and claim 47 specifies the vertebrate as a mouse or fish. Claim 27 of the copending application recites the same limitations as claim 45 except claim 27 more narrowly specifies a mouse, which encompasses the limitations of claims 45-47 of the instant claims. Claim 27 of the copending application also more narrowly specifies that stable integration is by homologous recombination and that the ubiquitous promoter be selected from the group consisting of polymerase I, II, and III dependent promoters.

Claim 48 of the instant application broadly encompasses an expression vector comprising a short hairpin RNA construct under control of a ubiquitous promoter. Claim 30 of the copending application encompasses the same limitations but also specifies that the expression construct comprise homologous sequences which integrate at a polymerase II dependent locus of the genome of the mouse. Claim 30 also specifies

that the ubiquitous promoter be selected from the group consisting of polymerase I, II, and III dependent promoters. Claim 30 of the copending application more narrowly encompasses a species of the instantly claimed expression vector of claim 48 of the instant application. Therefore, claim 30 encompasses the same limitations as instant claim 48.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCIA S. NOBLE whose telephone number is (571)272-5545. The examiner can normally be reached on M-F 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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1632

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